UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

**MEMORANDUM**

**Date: 3/11/2009**

**SUBJECT:** **Trichlorfon:** Human Health Risk Scoping Document in Support of Registration Review

**PC Code:** 057901
**Decision No.:** 399970
**Petition No.:** Not Applicable
**Risk Assessment Type:** Reg Review Scoping Document
**TXR No.:** Not Applicable
**MRID No.:** Not Applicable

**DP Barcode:** 356503
**Registration No.:** Not Applicable
**Regulatory Action:** Reregistration
**Case No.:** 0104

**CAS No.:** 52-68-6
**40 CFR:** 180.198

**FROM:** Thurston Morton, Chemist
Abdallah Khasawinah, Toxicologist
Health Effects Division (7509P)
Office of Pesticide Programs

**THRU:** Susan Hummel, Senior Scientist
Reregistration Action Branch IV
Health Effects Division (7509P)
Office of Pesticide Programs

**TO:** Kylie Rothwell, Chemical Review Manager
Special Review and Reregistration Division (7508P)
Office of Pesticide Programs

**Executive Summary**

Attached is Health Effects Division's (HED) human health risk scoping document for trichlorfon as part of the Registration Review process. Trichlorfon [dimethyl (2,2,2-trichloro-1-hydroxyethyl) phosphonate] is a selective organophosphate insecticide whose mode of toxic action is the inhibition of cholinesterase. It was determined to share a common mechanism with other organophosphates and was part of the organophosphate cumulative risk assessment which was completed in 2006. Trichlorfon is used to control a variety of arthropod pests including cockroaches, crickets, silverfish, bedbugs, fleas, cattle grubs, flies, ticks, leafminers, and leaf-hoppers. Tolerances for import purposes only (i.e., no U.S. registrations) for residues of

trichlorfon in/on food items are currently expressed in terms of trichlorfon *per se* [40 CFR §180.198]. Existing tolerances are 0.05 ppm for cattle fat, 0.02 ppm for cattle meat, and 0.01 ppm for cattle meat-by-products. Trichlorfon is available in granular, soluble concentrate, and wettable powder formulations. Trichlorfon is currently registered for non-agricultural uses such as golf course turf, ornamental shrubs and plants, and ornamental and baitfish ponds. Registered residential uses of trichlorfon include application to residential lawns. Although there are no registered agricultural or other food/feed uses in the U.S., trichlorfon is used in other countries as a pour-on treatment for cattle; this use is classified as a food use in the U.S. and requires a tolerance. Trichlorfon is not a restricted use pesticide and products are marketed for homeowner use.

The most recent comprehensive human health risk assessment for trichlorfon was conducted in support of the 2001 interim Tolerance Reassessment and Risk Management Decision (TRED) for trichlorfon (September 19, 2000 and supporting documents). Risk assessments were conducted for acute and chronic dietary exposure (food and water) in addition to residential and occupational exposure. Based on the dietary and drinking water analysis, acute and chronic dietary risks for trichlorfon for food only do not present risks of concern but there may be risks of concern when food and water are aggregated for children 1-6 years of age.

However, the Agency believes the modeled estimates for exposure to trichlorfon residues in surface water sources of drinking water, which exceed the Drinking Water Level of Comparison (DWLOC) by about two-fold, overestimate the dietary risk for several reasons as explained below (see page 8).

The occupational exposure assessment conducted for the 2001 TRED indicated risks of concern for exposure to occupational handlers. For mixer/loaders handling soluble powder for groundboom and chemigation application, the Agency expects that the changes to the use practice for golf course turf will mitigate worker risk concerns. Limiting the broadcast treatment to tees and greens is expected to reduce the amount of trichlorfon handled.

The ornamental post-application worker risk was a concern to the Agency for the application method assessed in the TRED. However, on December 20, 2000, Bayer Corporation informed the Agency that they would revise the use pattern for its soluble powder products and prohibit foliar application. Only direct application to soil at the base of the plant would be allowed for ornamentals, enabling the Agency to require a 12 hour REI. Prohibiting foliar application significantly impacts previous Margin of Exposure (MOE) estimates and restricted entry intervals (REIs). Direct soil application to ornamentals is expected to effectively mitigate risk concerns.

Mitigation measures presented in the trichlorfon TRED addressed exposures and risks associated with exposure to trichlorfon residues alone. Trichlorfon degrades to dichlorvos (DDVP), a registered organophosphate pesticide, in food, water, or the environment. As required under FQPA, the Agency estimated the aggregate risk from all sources of DDVP, including DDVP derived from trichlorfon, in its human health assessment for the 2006 Reregistration Eligibility Decision for DDVP. The Agency's assessment concluded that significant drinking water or inhalation exposure to DDVP is not expected from the use of trichlorfon on turf. However, the Agency required trichlorfon registrants to conduct several

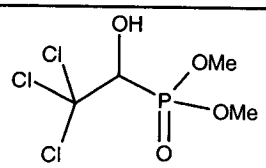
studies to confirm this conclusion: terrestrial field dissipation (835.6100); dermal exposure (875.2400); and inhalation exposure (875.2500). The registrant has submitted a waiver request based on the submission of additional data, for these studies. The Agency is in the process of reviewing this request. If it is determined, based on the results of these studies or other new information, that exposure to DDVP resulting from trichlorfon use presents potential risk concerns, the Agency will need to reevaluate the occupational exposure assessment for trichlorfon.

HED's problem formulation conclusions are as follows. 1) The toxicology endpoints for dermal and inhalation exposure need to be reassessed based on submission of new toxicity data. 2) The dietary exposure (food only) database is essentially complete. However, a new dietary exposure assessment including food and water will need to be conducted once new drinking water exposure estimates are obtained and residues of concern are confirmed. 3) The occupational/residential exposure assessments will need to be revised if toxicity points of departure change significantly. 4) The aggregate risk assessment will need to be revised once the new dietary exposure analysis is conducted. 5) An immunotoxicity study is required. This is a new data requirement under 40 CFR Part 158 for registration of a pesticide (food and non-food uses). 6) Comprehensive review of all available positive control data for the existing developmental neurotoxicity (DNT) study has been submitted and will be reviewed to fully satisfy the guideline requirement for the DNT study.

**Introduction**

HED has evaluated the existing human health risk assessments for trichlorfon to determine whether sufficient data are available and whether a new human health risk assessment is needed to support Registration Review. HED has considered the most recent risk assessments for trichlorfon, updates to its toxicity, exposure and usage databases, and current Agency science policies and risk assessment methods. Trichlorfon is a systemic insecticide currently registered for non-agricultural uses such as golf course turf, ornamental shrubs and plants, and ornamental and baitfish ponds. Registered residential uses of trichlorfon include application to residential lawns. There is also a foreign use of trichlorfon as a cattle pour-on, which is classified by the Agency as a food-use. The current tolerance is established for parent trichlorfon *per se* [40 CFR §180.198]. The residues of concern in food and water have not been determined due to an inadequate nature of the residue study in cattle. However, per the risk assessment conducted for the 2001 TRED, the residues of concern were determined to be trichlorfon and its metabolite dichlorvos.

## Chemical Identity

| Table 1. Trichlorfon Nomenclature | |
|---|---|
| Chemical structure |  |
| Common name | [dimethyl (2,2,2-trichloro-1-hydroxyethyl) phosphonate] |
| Empirical formula | $C_4H_8O_4Cl_3P$ |
| Molecular weight | 257.6 |
| PC Code | 057901 |
| IUPAC name | dimethyl (*RS*)-2,2,2-trichloro-1-hydroxyethylphosphonate |
| CAS name | dimethyl (2,2,2-trichloro-1-hydroxyethyl)phosphonate |
| Registration Review Case No. | 0104 |
| CAS registry number | 52-68-6 |

| PRODUCT (% a.i.)/ EPA REG. NO. | USES | APPL. METHOD(S) | MAX. SINGLE APPL. RATE | MAX YEARLY APPL. RATE/NO. OF APPL. | APPL. INTERVAL | RESTRICTIONS |
|---|---|---|---|---|---|---|
| Dylox 80 Concentrate 432-1298 | For formulation into end use products | N/A | N/A | N/A | N/A | Only for formulation into end-use products on lawns, turf, recreation areas, and ornamental lawns |
| Dylox 80 SP 432-1326 | Flowers, shrubs, and trees and recreational lawns and turf | Ground Aerial | 8.15 lb a.i./acre<br><br>*Narcissus* - 16 oz a.i./1,000 feet of row | For *Narcissus* – 1/year<br><br>All other use - Not specified | Not specified | - Do not apply directly to water… |
| Dylox 80 Turf and Ornamental 432-1289 | Landscape flowers, shrubs, trees, and landscape and recreational turf | Ground | 8.15 lb a.i./acre<br><br>*Narcissus* - 16 oz a.i./1,000 feet of row (repeat treatments annually) | 24.5 lb a.i./acre<br><br>No. of ApplicationsNot Specified | 7 days | - Do not apply directly to water…<br>- Do not apply within 25 ft of lakes, reservoirs, rivers, permanent streams, marshes, natural ponds, or estuaries.<br>- Do not apply through any type of chemigation system<br>- Golf courses: broadcast use is limited to tees and greens; use on fairways is limited to spot treatments<br>-432-1289 Watering in required for all uses, except foliar uses and for control of Lepidoptera and chinch bugs on turf.<br>-432-1464 for best results irrigate as soon as possible after application. |
| Dylox 420 SL 432-1464 | Landscape flowers, shrubs, trees, and landscape and recreational turf; golf course and residential turf | Ground | 7.6 lb a.i./acre<br><br>*Narcissus* – 16 oz a.i./1,000 feet of row | 24.5 lb a.i./acre<br><br>For *Narcissus* – 1 application/ year<br><br>All other use – No. of applications not specified | 7 days | |
| FL03001200 | Commercially-operated aquaculture production systems containing ornamental fish or non-food aquatic plants | Hand-held sprayer (systems less than 1 acre)<br><br>Truck-drawn sprayer (systems greater than 1 acre) | 0.25 mg a.i./L | Not specified | 14-days | None |
| AR98000300<br><br>MO99000500 | Commercially-operated ponds used for bait fish and ornamental fish production aquatic plants | Not specified (limited to ground equipment on Federal label) | 0.25 mg a.i./L | Not specified | Not specified (7-day interval on Federal label) | None |
| Dylox 6.2 Granular 432-1308 | Turfgrass | Ground | 8.10 lb a.i./acre | 24.5 lb a.i./acre<br><br>Max. no. of applications not secified | 7 days | - Do not apply directly to water<br>- Golf courses: do not apply within 25 ft of lakes, reservoirs, rivers, |

| PRODUCT (% a.i.)/ EPA REG. NO. | USES | APPL. METHOD(S) | MAX. SINGLE APPL. RATE | MAX YEARLY APPL. RATE/NO. OF APPL. | APPL. INTERVAL | RESTRICTIONS |
|---|---|---|---|---|---|---|
| **Granular** | | | | | | |
| The Andersons Tee Time Insecticide with 9198-110 **Granular** | | | | | | permanent streams, marshes, natural ponds, or estuaries<br>- Not for use on turf being grown for sale<br>- Must be watered in after application to move product into root zone<br>- Golf courses: broadcast use is limited to tees and greens; use on fairways is limited to spot treatments |
| Dylox Grub Control 432-1394 **Granular** | Lawns | Ground | 8.10 lb a.i./acre | Not specified | Not specified | - Do not apply directly to water<br>- Do not apply near fish pools, ponds, streams or lakes<br>- Water thoroughly within 24 hrs after applying |
| Dylox 9.3% Insect Granules 72155-83 **Granular** | Lawns (residential use only) | | | | | |
| Dylox Insect Granules 72155-33 **Granular** | | | | | | |

## Hazard Identification/Toxicology

The toxicology database provides evidence that cholinesterase inhibition is the most sensitive biomarker of exposure to trichlorfon in humans and laboratory animals. Trichlorfon, like other organophosphates, causes anticholinesterase and other neurotoxic effects in all species tested, including humans, monkeys, dogs, rabbits, rats, and mice. Neurotoxicity has been observed in acute, subchronic, chronic, and developmental/reproductive toxicity studies. In general, based on animal studies, trichlorfon is acutely toxic via the oral route of exposure (Category II), has low inhalation and dermal toxicity (Category III), causes eye irritation (Category II), and is a moderate skin sensitizer. It causes mild skin irritation.

Cholinesterase inhibition was the toxicity endpoint chosen for the acute and chronic dietary, and short- and intermediate- term dermal and inhalation risk assessments for occupational and residential exposure. The current points of departure are shown in Table 3.

Once the immunotoxicity study has been submitted and reviewed, HED will need to reexamine the endpoints and safety factors used for risk assessment purposes.

## Dietary Exposure

The only food use for trichlorfon is a foreign pour-on treatment for cattle, which then could be imported in the U.S. in the form of beef or beef byproducts. The nature of the residue in cattle is not completely understood and additional data are required. A residue analytical method as well as magnitude of residue data from dermal applications may be required if additional residues of concern other than trichlorfon *per se* are determined by the HED Residues of Concern Knowledge-Base Subcommittee (ROCKS). To compensate for inadequate data on the nature of the residue study and magnitude of residue study, HED has reassessed tolerances at the maximum level of trichlorfon *per se* found in a cattle nature of the residue study which was conducted at the same dermal dosing level as the magnitude of residue study (DDVP was not a significant residue in the metabolism study).

A chronic and acute dietary analysis was conducted using reassessed tolerances and percent of beef/veal imported, which was the only refinement utilized. The Biological and Economic Analysis Division (BEAD) provided information that the percent beef/veal imported into the United States has not changed significantly since the TRED. The acute dietary (food only) risk estimate for trichlorfon is below the Agency's level of concern at the 99.9th percentile [<100 % acute Population Adjusted Dose (aPAD)] for all population subgroups (17.6 % aPAD was occupied for Children 1-6 yrs, the most highly exposed subgroup). When compared to the chronic Population Adjusted Dose (cPAD) for trichlorfon, the estimated chronic dietary exposure based on reassessed tolerances for residues of trichlorfon is below HED's level of concern (<100 % cPAD) for all population subgroups (24.3 % cPAD for Children 1-6 yrs, the most highly exposed subgroup).

The acute and chronic dietary exposure from drinking water was conducted using DWLOCs in the Trichlorfon TRED. The estimated environmental concentrations (EECs) for surface water (GENEEC) were less than the chronic DWLOCs, except for Children 1-6 yrs, indicating that

chronic aggregate exposure to trichlorfon does not exceed HED's level of concern except for Children 1-6 yrs. when surface water is the source of drinking water. The EECs for surface water (GENEEC) were less than the acute DWLOCs except for Children 1-6 yrs, indicating that acute aggregate exposure to trichlorfon does not exceed HED's level of concern except for the highest exposed population (Children 1-6 years). The Agency believes the modeled estimates for exposure to trichlorfon residues in surface water sources of drinking water, which exceed the DWLOC by about two-fold, overestimate the dietary risk for several reasons: (1) the exposure model used to estimate surface water concentrations is a screening tool not well suited for estimating surface water concentrations resulting from a pesticide applied to turf, (2) the environmental fate properties for trichlorfon indicate that parent trichlorfon residues in surface waters are unlikely to reach consumers because of the rapid aerobic dissipation in the environment and (3)the modeling is based on golf course use; however, most trichlorfon use is in the residential setting (78%) while only 18% is used on golf courses. Residential use is likely to be random, varying from residence-to-residence, but will likely cover less acres in a single day than the golf course use. Lastly, the target MOE is 1000, providing an additional safety factor for children, which when combined with the conservatism in the modeled surface water and dietary assessments, provides high confidence that aggregate risks are not of concern. Confirmatory data are not required.

An updated drinking water assessment should be conducted for trichlorfon and the revised acute and chronic drinking water values incorporated directly into the dietary analysis, in accordance with current policy.

**Residential Exposure**

Residential Handlers

Potential trichlorfon residential use sites include lawns. Residential handler exposure to trichlorfon residues via dermal and inhalation routes can occur during handling, mixing, loading, and applying activities. The exposure duration of these activities was classified as short-term. MOEs are not of concern >1000.

**Short-Term Risk Characterization**:

Residential Post Application

For residential postapplication activities, the exposure duration is expected to be short- to intermediate-term. MOEs do not exceed HED's level of concern for adults and toddlers while either playing on treated lawns at both the low and high end estimates. Additionally, MOEs do not exceed HED's level of concern for adults playing 18 holes of golf on trichlorfon treated golf courses. MOEs do not exceed HED's level of concern for any of the incidental oral exposure scenarios for children playing on trichlorfon treated lawns at both the low and high end estimates.

**Aggregate Risk Assessment**

a. Acute Aggregate Risk Estimate and Exposure Assessment

Acute aggregate risk estimates exceed HED's level of concern for Children 1-6 years, if the source of water is surface water, but do not exceed HED's level of concern if the source of water is subsurface. Acute food exposure estimate does not exceed HED's level of concern. For the most highly exposed subpopulation, children 1-6 years old, 18 % of the aPAD is occupied. The EECs for surface water (GENEEC) were less than the acute drinking water levels of concern (DWLOCs) for all subpopulations except Children 1-6 yrs. Refinement using the PRZM-EXAMS (Tier II) surface water model is not possible due to the fact that an approved turf scenario in PRZM-EXAMS is not available. The EECs for groundwater (SCI-GROW) were less than the acute DWLOC's, indicating that acute aggregate exposure to trichlorfon in food and water is not of concern if the source of water is groundwater.

b. Short- to Intermediate-Term Aggregate Risk Estimates and Exposure Assessment

Several short to intermediate-term scenarios were identified: 1) Loading/Applying with a push type spreader to turf (8.2 lb ai/acre) aggregated with dermal postapplication exposure to an adult and 2) Toddler postapplication exposure aggregated with incidental oral hand-to-mouth exposure. When these scenarios are aggregated with chronic food and water exposure they do not exceed HED's level of concern.

c. Chronic Aggregate Risk Estimate and Exposure Assessment

Chronic aggregate risk estimates do not exceed HED's level of concern except for Children 1-6 years if the source of water is surface water. The chronic aggregate risk estimates do not exceed HED's level of concern if the source of water is subsurface. Chronic food exposure estimate does not exceed HED's level of concern. For the most highly exposed subpopulation, children 1-6 years old, 24 % of the cPAD is occupied. The EECs for surface water (GENEEC) were less than the chronic DWLOCs except for Children 1-6 years, indicating that chronic aggregate exposure to trichlorfon exceeds HED's level of concern for that subpopulation only, if the source of water is surface water. The EECs for groundwater (SCI-GROW) were less than the chronic DWLOC's, indicating that chronic aggregate exposure to trichlorfon in food and water is not of concern if the source of water is groundwater.

**Occupational Exposure**

HED has identified 10 major exposure scenarios for which there is potential for occupational handler exposure during mixing, loading, and applying products containing trichlorfon to non-agricultural use sites. These occupational scenarios reflect a broad range of application equipment, application methods, and use sites. The scenarios were classified as short-term and intermediate-term

The Agency had determined most exposure scenarios for trichlorfon do not result in risks that are of concern. The ant mound and house perimeter uses were voluntarily cancelled by the registrant to mitigate certain residential risk. Specific label changes were necessary in order for use on golf course turf and ornamentals and use in ornamental fish and bait ponds to be eligible for reregistration. Additionally workers were required to use a dust/mist respirator when mixing and loading the soluble powder formulation to address inhalation exposure associated with handling large volumes of pesticide for groundboom and chemigation applications. Therefore, of the ten scenarios originally evaluated for trichlorfon, six did not raise risk concerns and were eligible for reregistration without any changes to the registration. Two uses were voluntarily canceled to mitigate risk, and specific label changes were necessary for use on golf course turf (scenario 1) and use in ornamental fish and bait ponds (scenario 6) to be eligible for reregistration.

Occupational Post Application

The postapplication exposure to golf course workers who mow and maintain turfgrass on the day of application does not exceed HED's level of concern because the MOE is greater than 100. However, entry by workers in ornamental nurseries following treatments at an estimated 3 lb ai/-acre application rate do not reach a MOE of 100 until day 16. Furthermore, entry by workers in ornamental nurseries following treatments at an estimated 6 lb ai/acre application rate do not reach a MOE of 100 until day 23. These estimates for ornamental uses are based on HED's standard assumptions for dislodgeable foliar residues (20 % of application rate for initial residues and 10 % dissipation per day) because data for ornamental were not submitted. However, in the 2001 TRED, the Agency required trichlorfon registrants to amend labels to prohibit ornamental foliar application and only allow soil application at the base of the plant. Direct soil application to ornamentals is expected to effectively mitigate risk concerns.

**Public Health and Pesticide Epidemiology Data**

In October 2008, an updated review of trichlorfon incident reports was prepared by consulting the OPP Incident Data System (IDS) for reports of poisoning incidents occurring in the United States from 2000 to the present. The evaluation of incident data for trichlorfon has identified 25 incidents; symptoms appear generic and not confirmed to be related to exposure. There is no clear evidence of a trend or exposure pattern. Therefore, at this time, there are no remarkable case reports which suggest a plausible association between a moderate or severe health outcome and exposure to trichlorfon, nor can we discern any suggestion of a trend or pattern regarding the

health effects due to the alleged exposure to trichlorfon. The current review of the incident data does not warrant further investigation at this time. (M. Hawkins & J. Cordova, 10/30/2008).

**Tolerance Assessment and International Harmonization**

The tolerances listed in [40 CFR §180.198] are for residues of trichlorfon in/on animal products. A footnote must be added to the tolerance listing in [40 CFR §180.198] that states "There are no United States registrations for cattle commodities as of 6/24/99." The registrant is required to explain the difference in concentration of trichlorfon *per se* found in the magnitude of residue study in cattle versus the concentration of trichlorfon *per se* found in the nature of the residue in cattle study. Therefore, until an explanation is received and considered adequate, HED will reassess the tolerances for trichlorfon in cattle, fat; cattle, meat by products; and cattle, meat to the concentrations listed in following table. These concentrations were the maximum residues of trichlorfon *per se* in the nature of the residue in cattle study which was conducted at the same dermal dosing level as the magnitude of residue study.

Table 2. **Summary of US and International Tolerances and Maximum Residue Limits**

| Commodity | Tolerances or MRLs (ppm) | | | |
|---|---|---|---|---|
| | US | Codex | Canada | Mexico |
| Cattle, fat | 0.05 | None | None | None |
| Cattle, mbyp | 0.01 | None | None | None |
| Cattle, meat | 0.02 | None | None | None |

Note: The US tolerance definition includes the parent trichlorfon only. US tolerances are listed in 40 CFR 180.198.

There are no MRLs set for trichlorfon in Canada, Mexico, or through Codex; thus, there are no international harmonization issues to resolve.

**Environmental Justice**

Potential areas of environmental justice concerns, to the extent possible, were considered in the human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/nepa/tools/guidance/Volume1/2-6-EO_12898envjustice.pdf). The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

**Cumulative**

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. Trichlorfon is a member of the organophosphate common mechanism group. The most recent cumulative risk assessment for the organophosphates was published on July 31, 2006 and is available at

http://www.epa.gov/pesticides/cumulative/2006-op/op_cra_main.pdf. No cumulative risks of concern were identified in that assessment, and no additional mitigation was required for trichlorfon.

Prior to a final registration review decision for trichlorfon, the Agency will determine if there is any new information, such as new hazard or exposure data or information or changes to the use pattern, which would affect the cumulative risk assessment. Should the Agency determine that new information on trichlorfon is available which could potentially impact the cumulative risk assessment and result in a risk of concern, the Agency will revisit the cumulative risk assessment.

**Human Studies**

Trichlorfon risk assessments rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED) and the Outdoor Residential Exposure Task Force studies have been reviewed by the Agency and found on the basis of available evidence to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no barrier in EPA's "Protection of Human Subjects" regulation to reliance on these studies.

**Data Requirements**

Product chemistry:

98% T (EPA Reg.# 3125-9) - 830.7050 UV/Visible Absorption. **These data, required in the 2001 TRED, have been submitted and will be reviewed at a later time.**

Residue chemistry:

The nature of the residue is not adequately understood (T. Morton, D244279, 6/24/99). Additional data is required pertaining to the nature of the residue in animals (dermal treatment). Additional data may be required for storage stability, magnitude of residue in cattle (dermal treatment), and analytical method if additional residues of concern other than trichlorfon *per se* are determined by the HED ROCKS committee.

The registrant is required to explain the difference between concentration of trichlorfon *per se* found in the magnitude of residue study and that which was found in the nature of the residue study. **This requirement is still outstanding**

Toxicology:

Prenatal developmental toxicity study in rats (870.3700) – Previous study did not establish a NOAEL.

Developmental neurotoxicity study in rats – **The registrant submitted a DNT but its acceptability was pending due to a need for a comprehensive review of all available positive control data. These data have been submitted and will be reviewed at a later time.**

## References

| Author | Barcode | Date | Title |
|---|---|---|---|
| | | | |
| M. Hawkins and J. Cordova | None | 10/30/2008 | Updated Review of Trichlorfon Incident Reports |
| A. Khasawinah | D322591 | 8/22/2006 | Trichlorfon – Toxicology Study Reports |
| A. Khasawinah | D272254 | 7/26/2005 | Trichlorfon – Toxicology Study Reports |
| T. Morton | D273975 | 4/24/2001 | HED's Revised Drinking Water Levels of Concern and Aggregate Risk Assessment for Trichlorfon |
| T. Morton | D270439 | 11/30/2000 | HED's Revised Short- and Intermediate Term Aggregate Risk Assessment For Trichlorfon |
| T. Leighton | D270174 | 11/1/2000 | HED's Reassessment of the Use of ORETF Granular Push-Type Spreader Studies (LCO and Homeowner – MRID No. 44972201) for the Trichlorfon Risk Assessment |
| T. Morton | D268728 | 9/19/2000 | HED's Revised Preliminary Human Health Risk Assessment for Trichlorfon |
| T. Leighton | D264582 | 9/6/2000 | HED's Review of "Determination of Transferable Turf Residues on Turf Treated with Trichlorfon" |
| T. Leighton | D268695 | 8/30/2000 | HED's Insert to the Trichlorfon Risk Assessment: Residential Handlers and Postapplication Ornamental Uses |
| T. Leighton | D268125 | 8/9/2000 | HED's Revision of the Trichlorfon Residential Exposure/Risk Assessment |
| A. Khasawinah | D258023 | 8/9/1999 | The HED Toxicology Chapter for the Risk Assessment for the Reregistration Eligibility Decision Document |
| T. Leighton | D257671 | 7/11/1999 | Occupational and Residential Exposure Assessment and Recommendations for the Reregistration Eligibility Decision Document for Trichlorfon |

DCI Table

| **Guideline Number: 860.1300**<br>**Study Title: Nature of the Residue, Livestock** |
|---|
| **Rationale for Requiring the Data** |
| The Nature of the Residue in Livestock from dermal treatment with trichlorfon (GLN 860.1300) is not adequately understood. Trichlorfon, DDVP, O-desmethyl DDVP, dichloroacetic acid, dichloroethanol, and a polar compound were the tentatively identified/characterized residues. The polar compound at a retention time of 2-6 minutes must be identified in fat, kidney, and liver samples. Also a greater percentage of the total radioactive residue must be identified/characterized in the liver and muscle. The trichlorfon *per se* and DDVP concentration difference between the nature of the residue and magnitude of the residue studies must be explained. Both studies were conducted at 1X. |
| **Practical Utility of the Data** |
| **How will the data be used?**<br>The data will be used to provide a full characterization of the trichlorfon residue profile. If the nature of the residue data shows additional residues of concern, new tolerances may be needed for livestock commodities. In addition, a dietary exposure assessment will be conducted.<br><br>**How could the data impact the Agency's future decision-making?**<br>A dietary exposure assessment conducted utilizing the appropriate residue components and levels is required. Farmers and producers depend on EPA to set appropriate tolerances and levels. |

| **Guideline Number: 870.3700**<br>**Study Title: Prenatal Developmental toxicity (rat)** |
|---|
| **Rationale for Requiring the Data** |
| There is not an acceptable rat prenatal developmental toxicity study available for trichlorfon.<br><br>Trichlorfon is the primary residue of concern along with DDVP for both acute and chronic dietary exposure. The available prenatal developmental toxicity study in rats is unacceptable because a NOAEL could not be established. Since the RED was signed, the Agency has worked to finalize its update to the data requirements in 40 CFR part 158, which were promulgated in October 2007. Two developmental toxicity studies and a reproductive toxicity study are required for all use patterns. Given that children (1-6 years) represent the most highly exposed subpopulation for dietary risk from trichlorfon, the requested rat developmental toxicity study is needed to conduct a complete and comprehensive analysis of potential critical pre- and post natal toxicological effects. |
| **Practical Utility of the Data** |
| **How will the data be used?**<br>After review and evaluation of the prenatal developmental toxicity study, it is likely that the 10X database uncertainty factor would be reduced or removed. This would then impact the acute PAD. There is a possibility the acute PAD would increase by a factor of 10<br><br>**How could the data impact the Agency's future decision-making?**<br>If the acute PAD changes, then the dietary risk assessment would need to be revised. If the acute PAD increases by a factor of 10, then there is a decrease in risk. |

**Guideline Number: 870.7800**
**Study Title: Immunotoxicity**

**Rationale for Requiring the Data**

This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.

**Practical Utility of the Data**

**How will the data be used?**

Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).

**How could the data impact the Agency's future decision-making?**

If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Table 3. **Endpoint Selection Tables for Trichlorfon**

| EXPOSURE SCENARIO | DOSE (mg/kg/day) | ENDPOINT | STUDY | Target MOE |
|---|---|---|---|---|
| Acute Dietary | NOAEL=10<br>UF = 100<br>FQPA = 10 | Clinical signs, plasma, RBC and brain cholinesterase inhibition | Acute Neurotoxicity-Rat Study | Not Relevant |
| | **Acute RfD =0.1 mg/kg/day<br>AcutePAD = 0.01 mg/kg/day** | | | |
| Chronic Dietary | NOAEL=0.2<br>UF = 100<br>FQPA = 10 | Brain cholinesterase inhibition in both sexes | Chronic Toxicity-Monkeys | Not Relevant |
| | **Chronic RfD =0.002 mg/kg/day<br>ChronicPAD = 0.0002 mg/kg/day** | | | |
| Dermal Absorption | Estimated at 10% based upon the comparisons of LOAELs in the oral developmental toxicity (35 mg/kg/day) and the 21-day dermal toxicity (300 mg/kg/day) in rabbits. | | | |
| Short-Term (Dermal) | Dermal NOAEL=100 | Red blood cell cholinesterase inhibition | 21 Day Dermal - Rabbit | 100[b] |
| Intermediate-Term (Dermal) | Dermal NOAEL=100 | Red blood cell cholinesterase inhibition | 21 Day Dermal - Rabbit | 100[b] |
| Long-Term (Dermal)[a] | Oral NOAEL=0.2 | Brain cholinesterase inhibition in both sexes | Chronic Toxicity-Monkeys | 100 |
| Inhalation (Any Time Period) | Inhalation NOAEL= 0.0127 mg/L[c] | Plasma, red blood cell, and brain cholinesterase inhibition | 21-Day Inhalation-Rat | 100[b] |

[a] Since an oral value was selected, a 10% dermal absorption factor should be used for route to route extrapolation.
[b] Target MOE = 1000 for residential scenarios.
[c] 3.45 mg/kg/day = NOAEL(0.0127) * respiration rate of a young adult Wistar rat (8.46 L/hr) * study daily exposure duration (6 hr/day) ÷ body weight of a young adult Wistar rat (0.187 kg).

Toxicological Profile: Trichlorfon

| Type of Study/Guideline | Study Title | MRID No. | Results |
|---|---|---|---|
| 870.1100 | Acute Oral Toxicity-Rat | 00256446 | LD50=136 - 173 mg/kg Category II |
| 870.1200 | Acute Dermal Toxicity-Rat | 00090786 | LD50 ≥ 2 g/kg Category III |
| 870.1300 | Acute Inhalation Toxicity-Rat | 00256446 | LC50=533 mg/m$^3$ - 4 hours Category III |
| 870.2400 | Acute Eye Irritation-Rabbit | 41571302 | moderately irritating Category II |
| 870.2500 | Acute Dermal Irritation-Rabbit | 40306901 | non irritating Category IV |
| 870.2600 | Dermal Sensitization-Guinea Pig | 00257599 | Moderate contact allergen |
| 870.3200 | 21-Day Dermal Toxicity-Rabbit | 40306901 | Levels Tested: 0, 100, 300, 1000 mg/kg/day<br>Systemic NOAEL greater than highest dose<br>NOAEL for RBC was 100 mg/kg/day and the LOAEL for cholinesterase inhibition was 300 mg/kg/day based on significant inhibition in RBC cholinesterase activity |
| Non-Guideline | Comparative ChE Inhibition in maternal and fetal rats,(2005) | 46635501 | Levels tested 0, 150, 500, and 1750 ppm in the diet from GD 0-20 in 13 insemintaed female rats/dose.<br>No adverse clinical toxicity<br>NOAEL for maternal ChE activity inhibition was 150 ppm (10.4 mg/kg/day) and the LOAEL was 500 ppm (37.3 mg/kg/day).<br>Fetal LOAEL was 150 ppm (10.4 mg/kg/day) based on ChE activity inhibition in brain.<br>NOAEL was not determined. |
| Non-Guideline | Time Course ChE inhibition in young adult rats (2005) | 46647402 | Single oral dose at 0 or 75 mg/kg to 6 rats/sex/dose, sacrificed 1, 2, 4 or hrs later.<br>The peak of ChE activity inhibition occurred at 1 hr after dosing in plasma, RBC and brain.<br>Females were more affected than males |
| Non-Guideline | Acute ChE inhibition in young adult rats (2005) | 46647401 | Single oral dose at 0, 10, 25, or 50 mg/kg to 6 rats/sex/dose, sacrificed 1 hour post dosing.<br>LOAEL was 25 mg/kg based on brain ChE inhibition in females and the NOAEL was 10 mg/kg |
| Non-Guideline | Repeated dose ChE inhibition in young adult rats (2005) | 46635401 | Daily oral doses of 0, 5, 10, 20 or 40 mg/kg/day for 11 days to 6 rats/sex/dose.<br>Rats sacrificed 1 hour after the last dose.<br>LOAEL was 20 mg/kg/day based on brain ChE activity inhibition in males and females, and RBC ChE inhibition in females. The NOAEL was 10 mg/kg/day. |
| Non-Guideline | Acute Tox study to determine ChE peak inhibition in preweaning rats ((2005) | 46647404 | Single oral dose of 0 or 50 mg/kg to post natal day 11 rats, 9-10 rats/sex/dose and sacrificed at 1, 2, 4, 8 or 24 hours.<br>Peak ChE activity inhibition occurred at 1-2 hours post dosing |

| | | | |
|---|---|---|---|
| Non-Guideline | Acute oral tox study to determine ChE acitivy inhibition in preweaning post natal day 11 rats (2005) | 46647403 | Single oral dose of 0, 5, 10 or 30 mg/kg to 10 rats/sex. Sacrificed 2 hours post dosing. Acute LOAEL was 10 mg/kg based on ChE activity inhibition in plasma and brain in preweaning males and females. Acute NOAEL was 5 mg/kg |
| Non-Guideline | Repeated dose ChE inhibition in post natal day 11 rats (2005) | 46635601 | Daily oral doses of 0, 5, 10 or 20 mg/kg/day to 10 preweaning rats/sex/dose for 11 days, rats sacrificed 1 hour after the last dose. LOAEL was 5 mg/kg/day based on enzyme inhibition in brain ChE in females. A NOAEL was not established. |
| 870.6200 | Acute Neurotoxicity-Rat | 44578001 | Levels Tested: 0, 10, 50, 200 mg/kg<br>NOAEL was 10 mg/kg and the LOAEL was 50 mg/kg based on clinical signs, alterations in FOB, decreased motor activity, and significant plasma, RBC, and brain cholinesterase inhibition at 50 mg/kg |
| 870.6200 | Subchronic Oral Neurotoxicity-Rat | 43871701 | Levels Tested: 0, 6, 31, 165 mg/kg/day for males and 0, 7, 35, 189 mg/kg/day for females<br>The NOAEL for ChE inhibition was 6 mg/kg/day and the LOAEL was 31 mg/kg/day. The systemic and neurotoxic NOAEL was 31 mg/kg/day and the LOAEL was 165 mg/kg/day based on clinical signs in males and females, a slightly uncoordinated righting reflex in males, reduced motor and locomotor activity in males and females, and minimal myelin degeneration of the spinal nerve roots of males and females |
| 870.6300 | A developmental neurotoxicity screening study with technical grade trichlorfon 100% a.i. (Dylox®) in wistar rats (2003). Acceptable/Non-Guideline Pending review of positive control data. | 46205301 | Doses of 0, 150, 500 or 1750 ppm (equivalent to 0, 13.4, 49.0, and 145.6 mg/kg/day during gestation and 0, 33.1, 103.4, and 264.6 mg/kg/day during lactation) from gestation day (GD) 0 through lactation day (LD) 21. **The LOAEL for maternal systemic toxicity is 150 ppm (13.4 mg/kg/day; LDT) based on the inhibition of red blood cell ChE activity. A NOAEL for maternal systemic toxicity is not established.**<br>**The LOAEL for the offspring toxicity is 150 ppm (13.4 mg/kg/day) based on decreased startle amplitude in males and females on PND 22. An offspring NOAEL is not established.** |
| 870.6100 | 90-Day Delayed Neurotoxicity-Hen | 40351201<br>40879301 | Levels Tested: 0, 3, 9, 18 mg/kg/day<br>NOAEL was 9 mg/kg/day based on a slight effect on nervous tissue |
| 870.4300 | Chronic Feeding/ Carcinogenicity-Monkeys | 40776001 | Levels Tested: 0, 0.2, 1.0, 5.0 mg/kg/day<br>The LOAEL was 0.2 mg/kg/day based on |

| | | | |
|---|---|---|---|
| | | | findings of decreased plasma, RBC, and brain cholinesterase activity<br>Under the conditions of the study, the test material was associated with an increase in the incidence of benign pheochromocytomas in high dose males which was slightly outside of the historical control range. Since these tumors are very common in this strain of rats and were not present in the same strain at a higher dose level in another study (discussed below), they were not considered to be compound related by the HED Carcinogenicity Peer Review Committee (CPRC) |
| 870.3465 | 21-Day Inhalation-Rat | 00256446 | Levels Tested: 12.7, 35.4, 103.5 $mg/m^3$<br>NOAEL was 12.7 $mg/m^3$ and the LOAEL was 35.4 $mg/m^3$ based on inhibition of plasma, RBC, and brain cholinesterase activity |
| 870.3150 | Subchronic Toxicity/Dog | HED # 1668 & 1669 | Levels Tested: 20, 100, 300, 500 ppm<br>NOAEL was 20 ppm (0.5 gm/kg/day) and the LOAEL was 100 ppm (2.5 mg/kg/day) based on plasma and RBC cholinesterase activity. Brain ChE was not measured. |
| 870.4100 | Chronic Toxicity/Dog | 00090786 | Levels Tested: 0, 1.2, 6.3, 12.5, 25 mg/kg/day<br>The NOAEL was 6.3 mg/kg/day and the LOAEL was 12.5 mg/kg/day based on decreases in serum and RBC ChE activity |
| 870.4200 | Carcinogenicity/Mice | 40782401<br>40844301 | Levels Tested: 0, 45, 135, 405 mg/kg/day<br>In males, there was an increase in the incidence of hepatocellular adenomas at all dosed groups; however, the increase was not statistically significant. Based on the clinical signs of toxicity and the effects on ChE activity, it was determined by the HED Cancer Assessment Review Committee (CARC) that trichlorfon was tested at adequate dose levels. |
| 870.4300 | Combined Chronic Toxicity/ Carcinogenicity/Rat | 41056201<br>41973001 | Levels Tested: 0, 4.4, 13, 75 mg/kg/day for males and 0, 5.8, 17.4, 93.7 mg/kg/day for females<br>Chronic NOAEL was 4.4 mg/kg/day and the LOAEL was 13.3 mg/kg/day based on decreases in RBC and brain ChE levels and a significant increase in incidences of renal calcification in males<br><br>Levels Tested: 0, 129 mg/kg/day in males and 0, 159 mg/kg/day for females |

| | | | |
|---|---|---|---|
| | | | Compound related non-neoplastic lesions included duodenal hyperplasia, gastritis, pulmonary hyperplasia and inflammation, nasolacrimal inflammation, hepatocellular hyperplasia and vacuolation, chronic nephropathy and an increased incidence of dermal lesions were all reported at high dose. |
| 870.3700 | Developmental Toxicity/Rat | 40255601<br>41303201<br>41303202 | Levels Tested: 0, 45, 102, 227 mg/kg/day<br>The NOAEL for developmental and maternal toxicity were less than 45 mg/kg/day based on decreases in ChE activity in mothers and reduced ossification of sculls, vertebrae and sternebrae in fetuses |
| 870.3700 | Developmental Toxicity/Rabbit | 41565201 | Levels Tested: 0, 10, 35, 110 mg/kg/day<br>The NOAEL for maternal toxicity was 10 mg/kg/day and the LOAEL was 35 mg/kg/day. The NOAEL for developmental toxicity was 35 mg/kg/day and the LOAEL was 110 mg/kg/day |
| 870.3800 | 2-Generation Reproduction-Rat | 42228301 | Levels Tested: 0, 15, 50, 175 mg/kg/day<br>The parental LOAEL and NOAEL were 15 mg/kg/day and <15 mg/kg/day, respectively. The LOAEL for offspring toxicity was 175 mg/kg/day based on the presence of dilated renal pelvises and decreased weight of $F_1$ pups on days 7 and 21. The NOAEL for offspring toxicity is 50 mg/kg/day. No reproductive effects were observed. Therefore, the NOAEL was 175 mg/kg/day. |
| 870.5500 | Salmonella typhimurium gene mutation | 00249535 | trichlorfon was found to be weakly mutagenic at toxic concentrations with or without activation |
| 870.5575 | Sacharomyces cerevisiae gene mutation | 00256446 | trichlorfon was not mutagenic at levels up to 10,000 µg/ml, in either the presence or absence of activation |
| 870.5500 | Salmonella and E. coli gene mutation | 00028625 | trichlorfon was not mutagenic at levels up to 10,000 µg/ml, in either the presence or absence of activation |
| 870.5300 | in vitro cytogenic study in mammalian cells | 00028625 | trichlorfon, at doses ranging from 1 to 145 µg/ml, induced significant increases in mutation frequencies both with and without activation |
| 870.5550 | Unscheduled DNA synthesis in rat hepatocytes | 00028625<br><br><br><br>00256446 | trichlorfon induced unscheduled DNA synthesis in Wi-38 cells in the absence of S-9 activation (concentration from 0.1 to 10 mg/ml) but not with such activation<br><br>trichlorfon failed to in induce UDS in rat |

| | | | |
|---|---|---|---|
| | | | hepatocytes up to levels of severe toxicity |
| 870.5500 | Bacterial cells gene mutation | 00028625 | Trichlorfon (doses not stated) was positive for DNA damage and repair in S. typhimurium, but was negative in relative toxicity assays with E. coli and B. subtilis strains<br>trichlorfon was positive for mitotic recombination in the presence and absence of S-9 activation at concentrations from 10 to 50 mg/mL |
| 870.5900 | Sister Chromatid exchange | 40277201 | Trichlorfon induced sister chromatid exchange at 50 and 100 µg/ml in a dose dependent manner, but results were inconclusive in the presence of S-9 activation |
| 870.5900 | sister chromatid exchange in Chinese hamster ovary cells | 00028625 | Trichlorfon was associated with a marginal but significant increase in sister chromatid exchange in Chinese hamster ovary cells |
| | Clastogenicity in human lymphocytes | 40984701? | Trichlorfon was clastogenic in human lymphocytes in the absence of S9 activation at doses of 3, 10 or 30 µg/ml. |
| 870.5500 | Bacterial DNA damage/repair | 00256446 | In a recombinant DNA study conducted at doses of 3, 30 or 300 mg, trichlorfon did not inhibit the growth of Bacillus subtilis |
| 870.7485 | Metabolism Study- Rat | 40438101 | 80-90% of the test material was excreted within 24 hours. The major route of excretion was via the urine, followed by feces and expired air. One to 2% of the dose was found in the tissues after 96 hours. In this study, the metabolites were not adequately characterized. This study was classified as supplementary, but information was reported which could be used for regulatory purposes |

| **ORE Assessments Required for Existing Trichlorfon Uses** | | | | |
|---|---|---|---|---|
| **Use** | **Application Rate (lb ai/acre)** | **Application Methods** | **Handler Assessment Required?** | **Post Exposure Assessment Required?** |
| Turf | 8.1 | Ground | No – Previously assessed | No – Previously assessed. |
| Ornamentals | 6.0 | Ground | No – Previously assessed | No – Previously assessed |
| Narcissus | 0.9 # ai/100 gallons water as a drench per 1000 feet of row | Ground | No – Previously assessed | No – Previously assessed |
| Fish Ponds | 0.38 | Ground | No – Previously assessed | No – Previously assessed |